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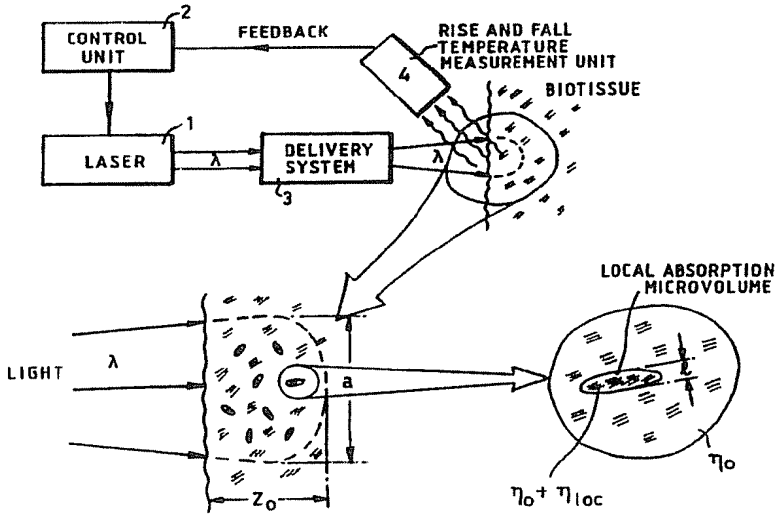

(57) Abstract

Photothermotherapy is effected by pulsed ultraviolet, visible or infrared laser radiation passing through a system (3) that assures the necessary laser pulse fluence to a biotissue treatment region. While the pulsed local heating of microregions in the tissue reaches therapeutic levels a unit (4) measuring the local heating by a single pulse and the average heating by a train of pulses controls, by way of feedback, a control unit (2) which determines the pulse energy and repetition period and the total exposure dose to provide a required therapeutic effect without risk of thermal damage to the exposed tissue region.

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A DEVICE AND METHOD FOR LASER PHOTOTHERMOTHERAPY

The present invention relates to a device for laser photothermotherapy comprising a pulsed laser constructed to operate in the ultraviolet, visible or infrared portion of the spectrum, and a system arranged to deliver pulsed irradiation generated from said laser to a targeted area of living human or animal tissue.

All devices and methods of using laser light for therapeutic and surgical purposes can be divided into two classes, depending on whether the laser-exposed biotissue suffers thermal damage upon absorption of radiation or not. Such a classification embraces all types of lasers, both pulsed and continuous-wave, for which the maximum permissible heating temperature of biotissue that still does not cause damage depends on the length of time that the biotissue stays heated.

The non-destructive class includes devices and methods which use low-intensity laser or incoherent radiation causing biostimulation without perceptible heating and find successful application in curing many a disease (the photomedical fundamentals of the method have

been described in Laser Science and Technology - An International Handbook, Vol.8 (Harwood Acad. Publ., 1989) p189 under the heading Photobiology of Low-Power Laser Therapy by T T Karu). Means for phototherapy with low-intensity light are the subject-matter of a number of inventions by Omega University Technologies Limited. This class also includes photodynamic therapy means and methods which utilize the photochemical action of sensitizers introduced in biotissue.

The destructive class includes devices and methods which use high-intensity continuous-wave or pulsed radiation causing a substantial heating of biotissue. High-intensity continuous-wave laser radiation absorbed by biotissue causes its heating and destruction (coagulation, carbonization, pyrolysis, and evaporation as temperature grows higher). This is employed in the laser thermal surgery of soft biotissue. High-intensity pulsed laser radiation at a wavelength of strong absorption by biotissue causes its high pulsed overheating, followed by vaporizing ablation. This is used for destruction of biotissue, both soft and hard (bones, atherosolerotic plaques).

An object of the present invention is to provide a device and method for photothermotherapy whereby high-intensity laser radiation can be absorbed by biotissue in controlled conditions without unsatisfactory heating of the entire laser-exposed volume of biotissue.

According to the invention, a device for laser photothermotherapy as defined in the first paragraph of this specification is characterised in that control means are provided for controlling said laser to generate pulses of variable duration, repetition rate and pulse duration between the pulses, and that measuring means responsive to the tissue, when irradiated, are provided for operating said control means for the pulse duration and wavelength delivered by said laser to correspond to

exogenous or endogenous chromophores in the tissue, said measuring means being responsive to local microheating of an absorbing said chromophore or chromophores and the surrounding local microregion, significantly higher than the average temperature of the entire targeted tissue, for actuating said control means to render the pauses between consecutive laser pulses to be sufficiently long to permit cooling of the temperature elevation in said local microregion between each pulse and the next.

A chromophore is defined as a molecule that absorbs light at a specific wavelength.

According to another aspect of the invention, a method of laser photothermotherapy comprises delivering ultraviolet, visible or infrared laser pulse energy to a targeted area of living human or animal tissue by means of the device defined above.

In order that the invention may be clearly understood and readily carried into effect, a device and a method in accordance therewith will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 is an explanatory graph showing tissue destruction as a function of time and temperature;

Figure 2 is a graph relating laser pulse fluence or radiation energy density and laser pulse duration and showing regions of laser radiation parameters;

Figure 3(a) is a graph showing laser light intensity as a function of time;

Figure 3(b) is a graph showing bio-tissue temperature variation in relation to laser pulses; and

Figure 4 is a schematic diagram of a device for photothermotherapy.

Referring to Figure 1, the area beneath the curve covers the range of relationships between temperature and duration whereby permissible heating temperture of bio-tissue can be effected without causing damage to the

tissue.

In Figure 2 the region I covering laser photochemical reactions that are non-destructive (as well as photodynamical therapy and biostimulation) is related to the curve of Figure 1. The parameter range of radiation of laser surgery is denoted by region II in Figure 2 where high-intensity continuous-wave laser radiation absorbed by bio-tissue causes its heating and destruction as by vaporization and coagulation. The parameter region of laser radiation for ablation surgery is denoted by symbol III in Figure 2. Both regions II and III constitutute the destructive class of laser photochemical reactions.

Recent investigations have revealed that account should be taken of the spatial absorption inhomogeneity of biotissue. The presence in biotissue of local microregions containing one or more chromophores characterised by increased absorption at certain radiation wavelengths makes it possible to effect their pulsed overheating without their being damaged and without any noticeable heating of the entire laser-exposed volume of biotissue. It is precisely this distinctive feature of biotissue that allows laser phototherapy to be implemented. The parameter region of radiation for laser photothermal therapy is denoted by symbol IV in Figure 2. The radiation parameters necessary for laser phototherapy differ from those for the other laser therapy (region I) and surgery (regions II and III) methods indicated above.

Arguments in favour of the existence of such a laser photothermotherapy method will now be given and the choice of the parameters of a means for its implementation explained. Biotissue is characterised by its volume-averaged absorption per unit length, η_o, and attenuation per unit length, A, which somewhat exceeds η_o because of scattering. As a result, laser

radiation penetrates biotissue to a depth of $z_o \simeq 1/A$. Owing to absorption of radiation, biotissue gets heated by an amount of Δ T, and then cools by diffusion during the time

$$\tau_{cool} = z_o^2/4X \qquad (1)$$

where X is the thermal diffusivity, and the laser beam diameter a is taken, for the sake of definiteness, to be greater than z_o. By way of illustration, let us consider soft biotissue with $A \simeq 10\ cm^{-1}$ and $X \simeq 1.3 \times 10^{-3}\ cm^2/s$. The cooling time in this case is $\tau_{cool} \simeq 2$ s. Consequently, by using a laser pulse with a duration of $\tau_p < \tau_{cool}$ one can, according to the data of Figure 1, heat the tissue by $\Delta T_{max} = 5\text{-}10^{o}C$ without running any risk of it being damaged. This limits the fluence of a laser pulse with a duration of $\tau_p < \tau_{cool}$ to a value of

$$\phi < \phi_{max} \simeq \Delta T_{max} \rho c/\eta_o \qquad (2)$$

where ρ and c are the density and heat capacity of biotissue, respectively, and $\eta_o < A$. In our example, $\phi_{max} \simeq 4\ J/cm^2$, which corresponds to a maximum permissible average laser intensity of $I_{max}^{av} = \phi_{max}/\tau_{cool} \simeq 2\ V/cm^2$

Biotissue has local absorption inhomogeneities of varying size: of the order of a few nanometers (biomolecules), a few tens of nanometers (biomolecular aggregation, membrane thickness), a few microns (cells and subcellular units), and more (microcapillaries). If a local absorption microregion has an absorptivity of $\delta\eta_{loc}$ exceeding the volume-averaged absorptivity η_o, it can be heated with a laser pulse by an amount of δT_{loc} exceeding the volume-averaged heating Δ T. The cooling time τ_{loc} of the local overheating microregion is determined by its size l:

$$\tau_{loc} \simeq I^2/4x \qquad (3)$$

If the laser pulse duration τ_p is shorter than this cooling time, the amount of local overheating will then be

$$\delta T_{loc} = \Delta T(\delta\eta_{loc}/\eta_o) \qquad (4)$$

For example, the cooling time of a local absorption microregion of size $l \simeq 30$ nm $= 3\times10^{-6}$ cm is $\tau_{loc} \simeq 2\times10^{-9}$ s. Consequently, to effect a pulsed local heating of such a microregion, the duration τ_p of the laser pulse used must be shorter than 2 ns. If the laser pulse fluence permissible from the standpoint of the volume-averaged non-destructive heating is, according to the above numerical example, $\phi_{max} \simeq 4$ J/cm^2, the peak intensity of the ultrashort laser pulse is $I_p \simeq \phi_{max}/\tau_p \simeq 2 \times 10^9$ W/CM^2. This intensity value is quite permissible, but it is fairly close to the threshold marking the onset of multiple-photon absorption effects. Even if the contrast of local absorption against the background of average absorption, $K=\delta\eta_{loc}/\eta_o$ is low, one can achieve a noticeable pulsed overheating ($\delta T_{loc} \simeq$ = 15-50^o) of local absorption microregions for a time of $\tau_{loc} \simeq$ 2 ns, the average heating of biotissue being quite insignificant ($\Delta T \simeq$ 5-10^{o}C). The time interval between successive ultrashort laser pulses, τ_{rep}, must be longer than the cooling time τ_{cool} of the entire laser-exposed bulk of biotissue. In the above numerical example, $\tau_{cool} \simeq 2$ s.

To effect a selective pulsed heating of microregions of smaller size, the laser pulse duration must be shorter, in accordance with equation (3), and to prevent multiple-photon effects in the bulk of biotissue, the laser energy must be distributed among several pulses

within the time interval τ_{cool}, so as to ensure that the peak intensity does not perceptibly exceed the value of $I_p \simeq 2 \times 10^9$ W/cm^2. Similarly, to achieve a local pulsed heating of larger microregions, one can use, in accordance with equation (3), longer pulses, and since the peak laser intensity will be lower than 10^9 W/cm^2, radiation energy can be deposited in biotissue with single pulses. The interval between them in this case must not exceed τ_{cool} in order to avoid destructive volume-averaged heating of biotissue. Figure 3a shows the laser pulse sequence and Figure 3b, the temporal variation of the temperature of the exposed medium, caused by both the local heating $\delta \tau_{loc}$ of the microregions of increased absoption and the volume-averaged heating ΔT of the tissue. The volume-averaged laser heating can accumulate during a long period of τ_{cool}, if the cooling time is much longer than the interval τ_{rep} between the pulses. At the same time, the local heating of the microregions of increased absorption rapidly vanishes within the time $\tau_{loc} << \tau_{rep}$. The average heating ΔT of the exposed region during the time τ_{cool} must not exceed a maxium value of ΔT_{max}.

The therapeutic effect of laser pulses is due to, first, the local pulsed non-destructive heating of microregions in the laser-exposed biotissue by the amount defined by equation (4) and secondly, the production of the pulsed temperature gradients

$$d\Delta T/dz \simeq \delta \tau_{loc}/l = (\Delta T/l)(\delta \eta_{loc}/\eta_o) \qquad (5)$$

that no other method can provide. Both these effects influence materially the course of metabolic processes on the molecular, subcellular, cellular, and above-cellular levels.

The above arguments define the region of laser radiation parameters with which pulsed laser

photothermotherapy can be realised. This region is denoted by the symbol IV in Figure 2. These considerations also determine the choice of the parameters the device for implementing the technique must have.

A device for laser photothermotherapy is shown in Figure 4 and includes a pulsed laser 1 whose wavelength λ corresponds to that of local absorption by microregions of average size $l(\lambda)$ in biotissue, a laser pulse duration control unit 2 providing for the generation of laser pulses with a duration of τ_p satisfying the condition

$$\tau_p < \tau_{loc} = l^2(\lambda)/4X \qquad (6)$$

and a repetition period of τ_{rep} meeting the requirement for the absence of any noticeable volume-averaged heating of biotissue:

$$\tau_{rep} < \tau_{cool} = z_o^2(\lambda)/4X \ll 1/[4\eta_o^2(\lambda)]X \qquad (7)$$

a delivery system 3 to deliver radiation to a biotissue treatment region that ensures the necessary laser pulse fluence

$$\phi_p \simeq \Delta T_{max}\, pc/\eta_o \qquad (8)$$

with which the volume-averaged heating of biotissue falls within permissible limits, ΔT_{max}, while the pulsed local heating of the microregions in the tissue reaches therapeutic levels ($\delta T_{loc} > 15\text{-}50^{\circ}C$), and a rise and fall measurement unit 4 for measuring the local heating by a single laser pulse and the average heating ΔT by a train of laser pulses, which controls, by way of feedback to the control unit 2, the pulse energy and repetition period and the total exposure dose in order to provide for therapeutic effect without running the risk of

thermal damage to the exposed tissue region. For this purpose, use can be made, for example, of a small-time-constant radiometer registering the heat emission intensity of the heated tissue regions. To measure the pulsed heating of local microregions, use is made of the fast component (1 in Figure 3b) of the temperature variation following the laser pulse, whereas the volume-averaged heating is determined from the slow temperature variation component (2 in Figure 3b).

It will be understood that the construction and parameters of the units 1, 2, 3, 4 will be clear to those skilled in the associated art and, therefore, do not require detailed description in this specification.

Table 1

An example of selecting laser pulse parameters for the laser photothermotherapy of biotissue with η_o = 10 Cm^{-1} and X = $1.3x10^{-3}$ cm^2/s as a function of the average size 1(λ) of local microregions of increased absorption

1(λ)	300 nm	30 nm	10 nm	3 nm
τ_{cool}, s	2	2	2	2
Φ_{max}, j/cm^2	4	4	4	4
I_{max}^{av}, W/cm^2	2	2	2	2
τ_{10c}, s	$2x10^{-7}$	$2x10^{-9}$	$2x10^{-10}$	$2x10^{-11}$
τ_p, s	< $2x10^{-7}$	< $2x10^{-9}$	< $2x10^{-10}$	< $2x10^{-11}$
τ_{rep}, s	2	2	0.2	0.02
Φ_p, j/cm^2	4	4	0.4	0.04
I_p, W/cm^2	$2x10^7$	$2x10^9$	$2x10^9$	2.10^9

Table 1 lists the laser pulse parameters necessary for treating biotissue, for example, with an absorptivity of η_o = 10 cm^{-1} and a thermal diffusivity of X = $1.3x10^{-}$

^{3} cm^2/s, as a function for the average size l (λ) of local microregions of increased absorption at the laser wavelength λ . For l > 30 n = 300 A, the laser pulse repetition period is determined by the cooling time τ_{cool}, whereas for l < 30 n, the pulse repetition period is selected to be shorter in order to limit the peak pulse intensity to a non-destructive level of some $2x10^9$ W/cm^2. In that case, the laser pulse fluence is limited to a safe average heating level of around 4 J/cm^2.

The device can also be used in a method of laser photothermotherapy where tissue is injected by exogenak non-toxic dye or drug comprised by chromophores of suitable size to enable local micro-heating, on absorbing the effective wavelength, of the microregion where the chromophores of the dye or drug are situated and cause therapeutic or destructive effects according to the condition treated.

CLAIMS:

1. A device for laser photothermotherapy comprising a pulsed laser constructed to operate in the ultraviolet, visible or infrared part of the spectrum, and a system arranged to deliver pulsed irradiation generated from said laser to a targeted area of living human or animal tissue, characterised in that control means (2) are provided for controlling said laser (1) to generate pulses of variable duration, repetition rate and pause duration between the pulses, and that measuring means (4) responsive to the tissue, when irradiated, are provided for operating said control means for the pulse duration and wavelength delivered by said laser to correspond to the size and nature of one or more targeted absorbing exogenous or endogenous chromophores in the tissue, said measuring means being responsive to local microheating of an absorbing said chromophore or chromophores and the surrounding local microregion, significantly higher than the average temperature of the entire targeted tissue, for actuating said control means to render the pauses between consecutive laser pulses to be sufficiently long to permit cooling of the temperature elevation in said local microregion between each pulse and the next.

2. A device according to Claim 1, characterised in that said measuring means (4) comprises a short-time constant radiometer arranged to register the heat emission of the tissue region, when targeted, the radiometer comprising a fast component to measure pulsed heating of local microregions following each laser pulse and a slow temperature variation component for detecting volume-averaged heating of the targeted area.

3. A device according to Claim 1 or Claim 2, characterised in that said control system is contrived for each pulse to have a duration complying with the relation

$$\tau_p < \tau_{ac} = I^2(\lambda)/4\chi$$

and for each pulse to have energy complying with the relations

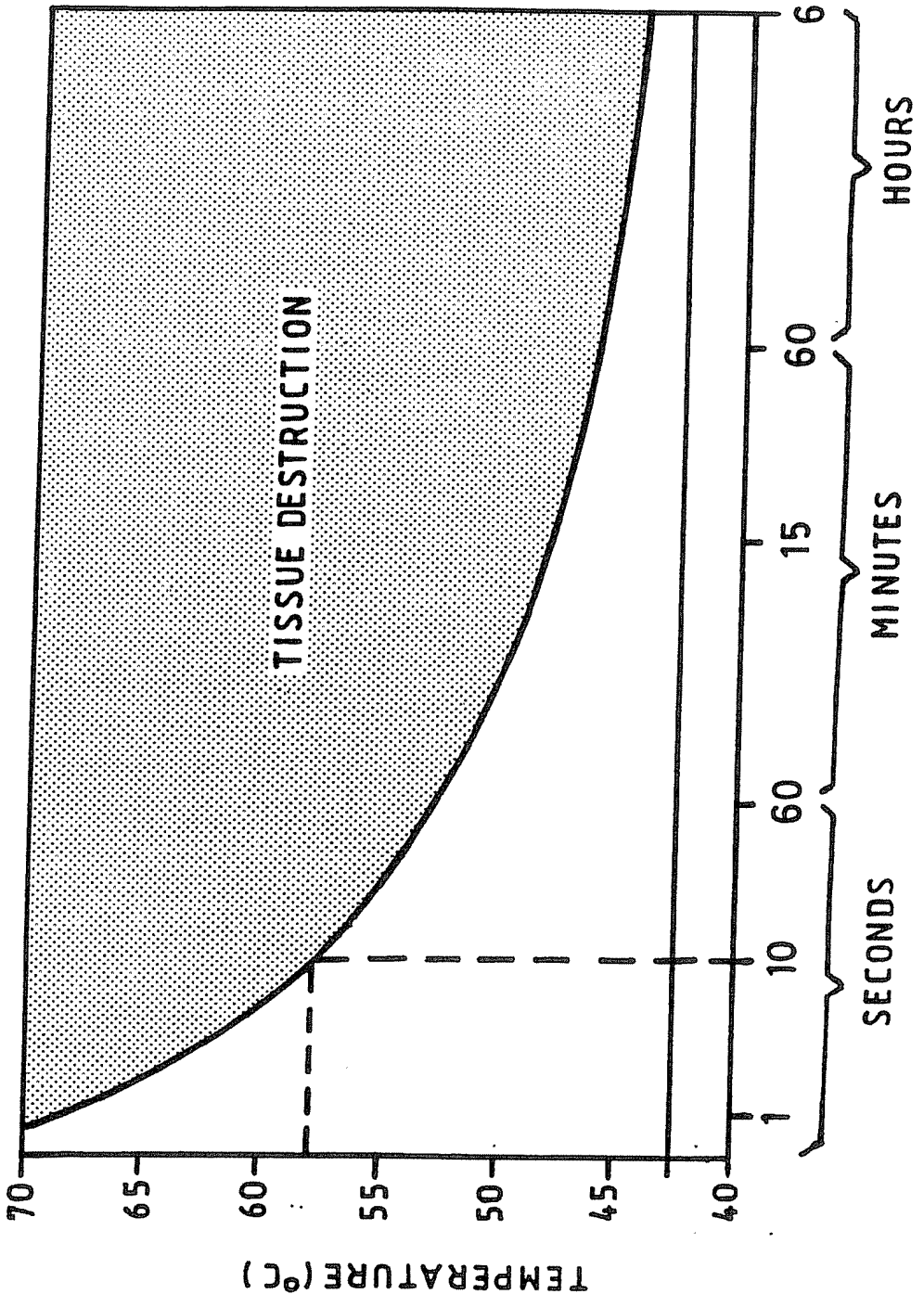
$$\phi < \phi_{max} \simeq \Delta T_{max}\, pc/\eta$$

and

$$\delta T_{loc} = \Delta T\, (\delta\eta_{loc}/\eta_o)$$

4. A method of effective laser photothermotherapy comprising delivering ultraviolet, visible or infrared laser pulse energy to a targeted area of living human or animal tissue characterised in that the method is effected by means of a device according to any one of the preceding claims.

FIG.1.



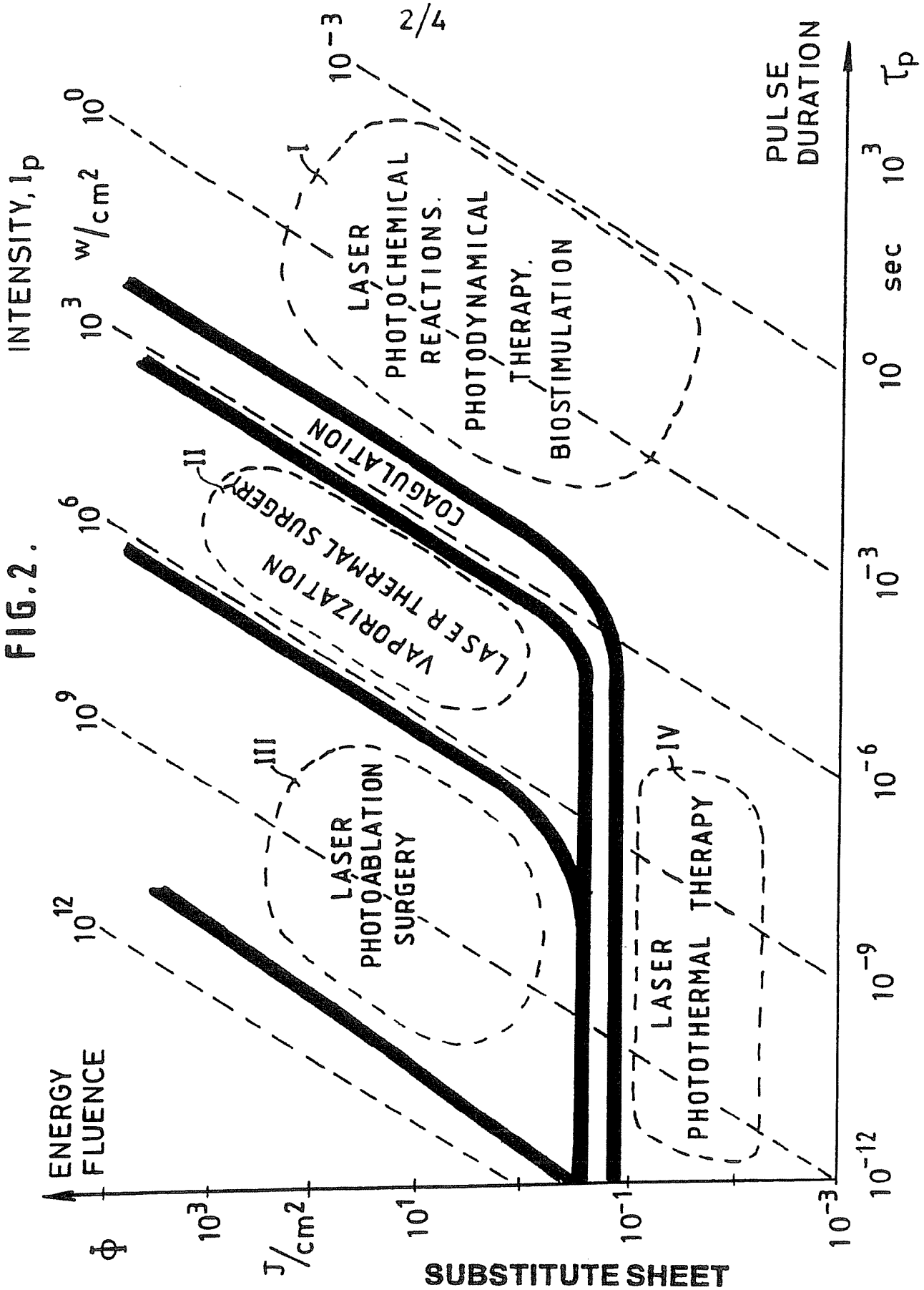


FIG. 2.

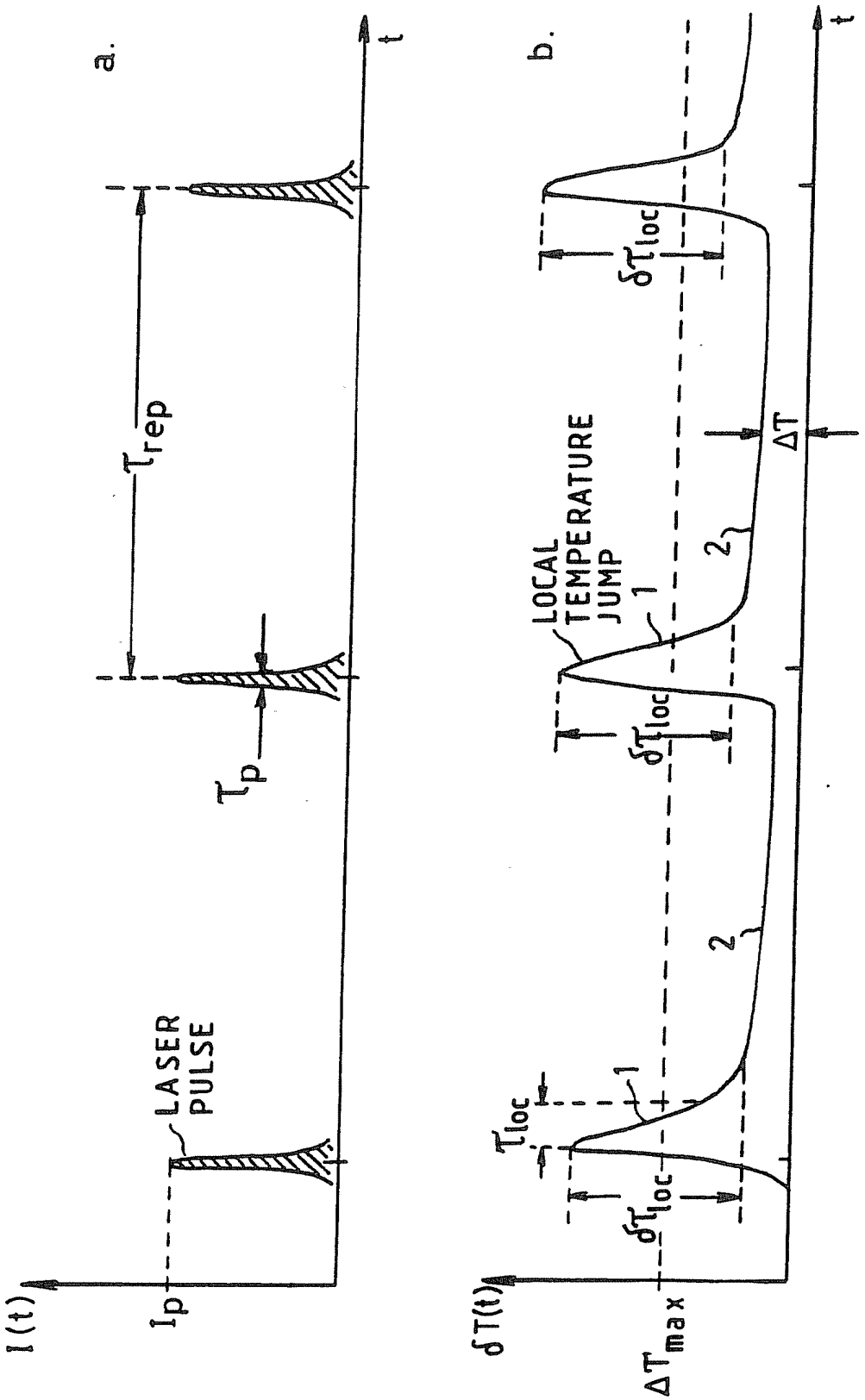
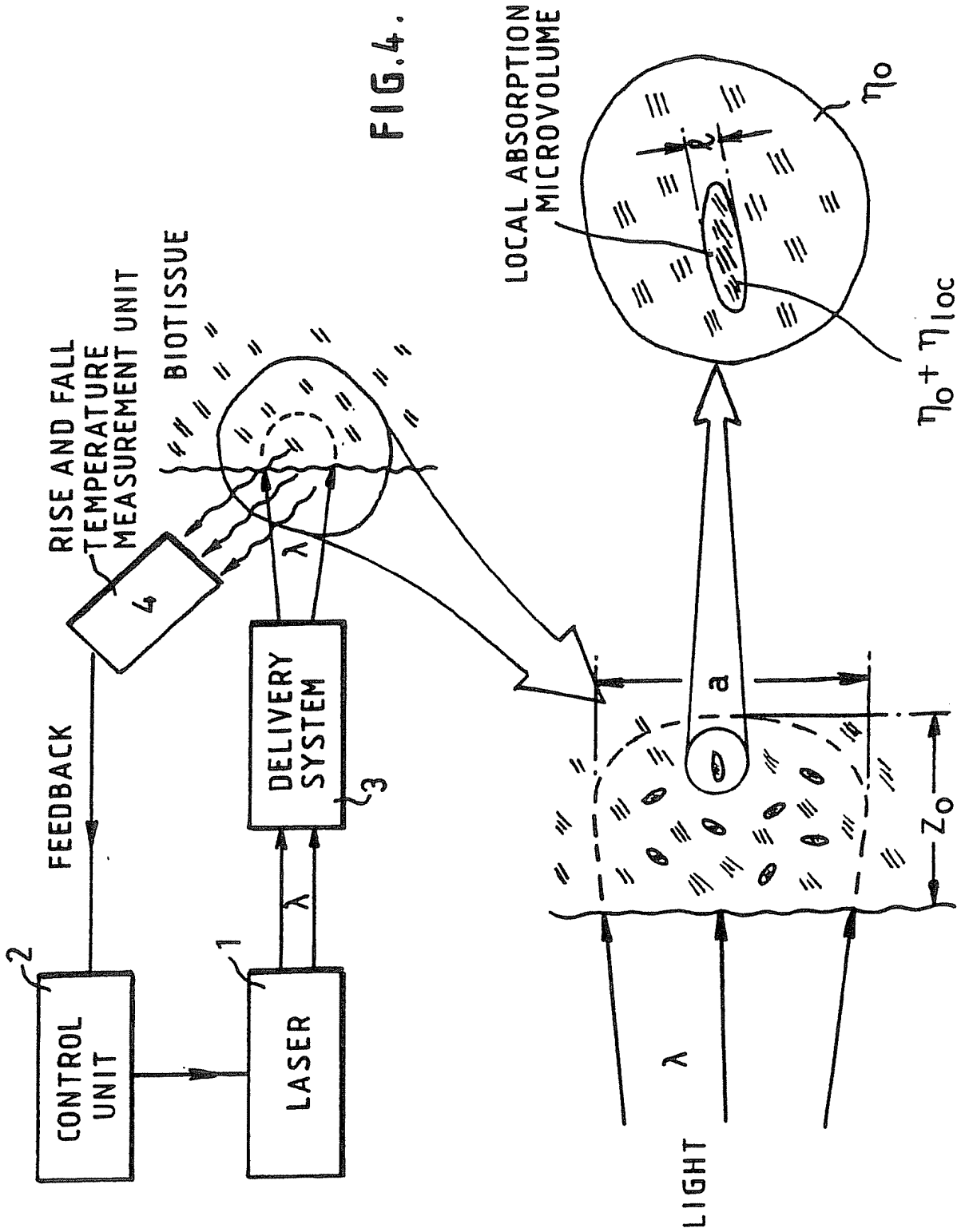


FIG.3

FIG.4.



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Appli n No PCT/GB 91/00862

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 N 5/06 A 61 N 5/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A,P	US,A,4950268 (RINK) 21 August 1990, see column 5, line 64 - column 7, line 3	1
A	DE,A,3134953 (SCHMID) 10 March 1983, see pages 5-8	1
A	WO,A,8600515 (THE JOHNS HOPKINS UNIVERSITY) 30 January 1986, see page 16, line 32 - page 20, line 10	1
A	GB,A,2000335 (R.C.A.) 4 January 1979, see page 2, lines 39-58	2

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13-09-1991	21. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 4 because they relate to subject matter not required to be searched by this Authority, namely:

see PCT Rule 39.1 (iv)

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6 4(a)

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100862 SA 48153

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/09/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4950268	21-08-90	US-A- 4848339	18-07-89
		US-A- 4994060	19-02-91
DE-A- 3134953	10-03-83	None	
WO-A- 8600515	30-01-86	US-A- 4592361	03-06-86
		EP-A,B 0187853	23-07-86
		JP-T- 61503005	25-12-86
GB-A- 2000335	04-01-79	US-A- 4190053	26-02-80
		DE-A,C 2827003	21-12-78
		FR-A,B 2395039	19-01-79
		JP-C- 1157766	25-07-83
		JP-A- 54007789	20-01-79
		JP-B- 57053110	11-11-82

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